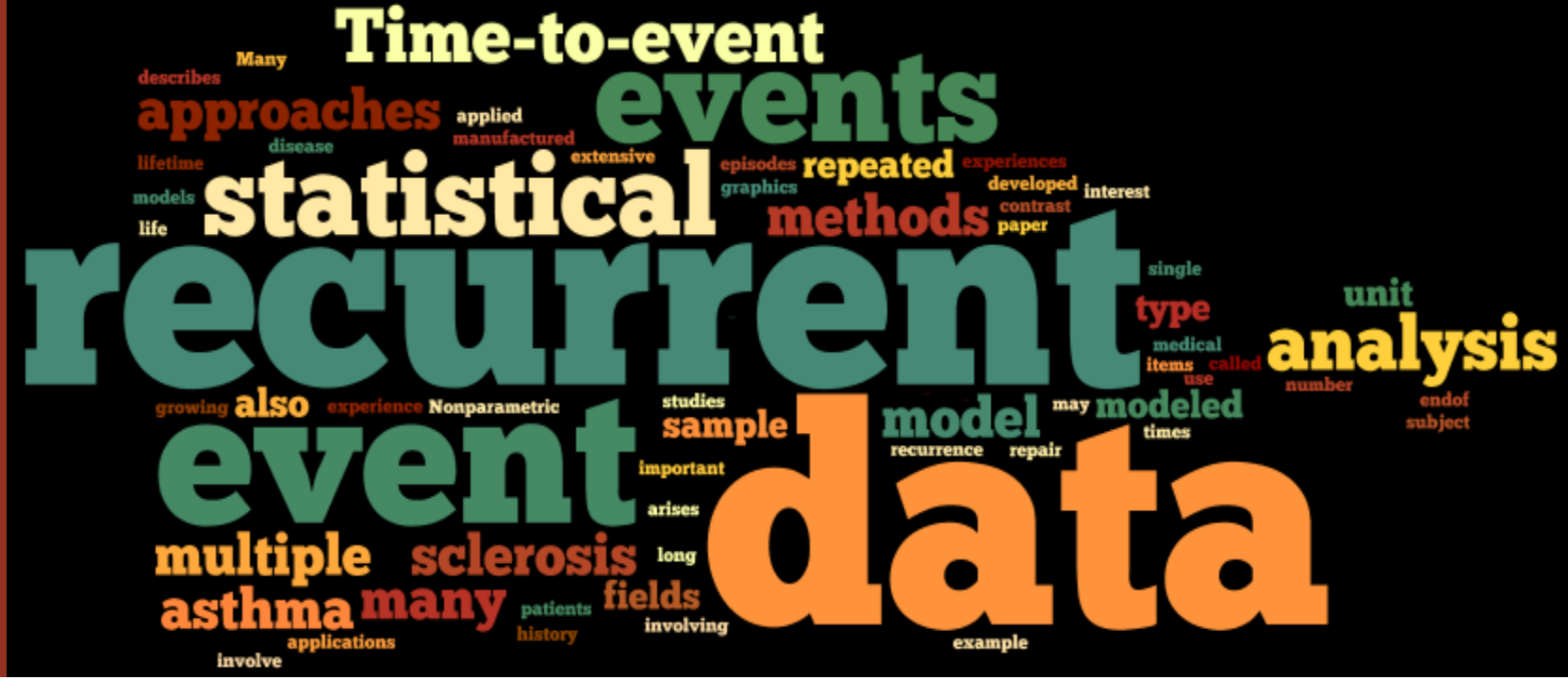

Recurrent event endpoints in cardiovascular outcome trials – What is the estimand of interest?

Mouna Akacha and Guenther Mueller-Velten – Novartis Pharma AG

PSI/BBS Meeting - September 14th , 2016

Acknowledgments

- Jim Gong
- Marty Lefkowitz

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Outline

- Background
- Clinical relevance of recurrent events
- Challenges – how to deal with death?
- Estimand framework
- Estimands in the recurrent event data context
- Case study in chronic heart failure
- Conclusions

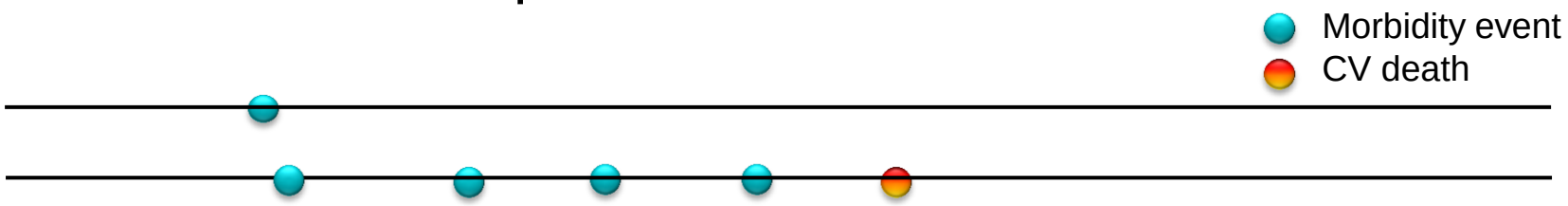
Traditional approach in CV outcome studies

- Time-to-first event approach commonly used for a composite of disease-related morbidity and mortality (M&M) endpoints
  - Used in many trials that have changed the practice of cardiovascular medicine
  - Attempts to measure the “overall benefit”
  - Avoids competing risk and multiplicity problem (morbidity/mortality)

Limitations of time-to-first event approach

Wu & Cook (2010), Neaton et al (2005)

- Focuses on the first event and ignores repeated events, which can lead to a substantial loss of information
  - Not even all disease related deaths are counted
- A patient with a single early non-fatal morbidity event may be considered worse than a patient with multiple morbidity events and subsequent CV death



- Clinical interpretation of treatment effect requires component analysis

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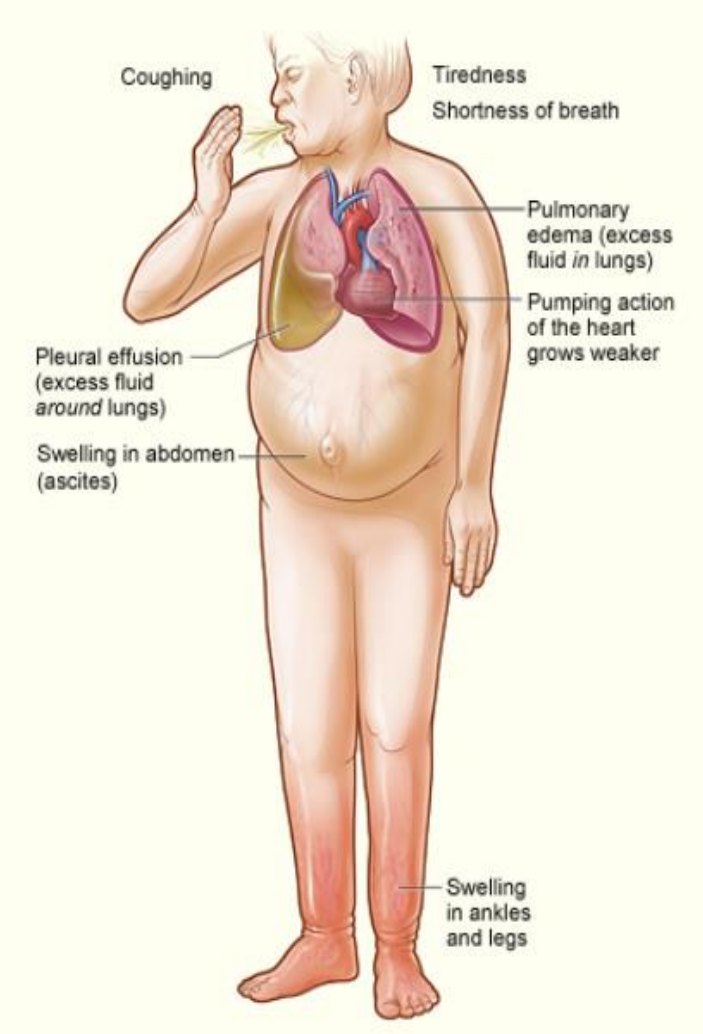
Chronic heart failure (CHF)

Focus on CHF but same ideas apply to other CV indications

- Heart Failure (HF) is a common and global health problem
  - It affects approx. 1-2% of adults in developed countries
- HF is an abnormality of cardiac structure and/or function
  - Leads to pump failure and insufficient delivery of blood around the body
  - Symptoms include shortness of breath, excessive tiredness and leg swellin.
- HF is a very serious condition
  - High mortality rate
  - Recurrent heart failure hospitalizations (HFH)



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Recurrent event endpoints

- Utilize substantially more HFH **and** CV deaths than time-to-first event approach
- Contributions of CV mortality to primary composite endpoints are similar in time-to-first event and in recurrent events analyses

Table I Number of events in 'time-to-first event' analysis and 'recurrent events' analysis of heart failure trials

Trial	Time-to-first-event (CV death or HF hospitalization): CV death as % of primary outcome (*n*/*n* = *N*)	Recurrent events (all CV deaths and all HF hospitalizations): CV death as % of all events (*n*/*n* = *N*)
CHARM-Added	316/705 = 1021 (31.0%)	649/1443 = 2092 (31.0%)
CHARM-Alternative	237/503 = 740 (32.0%)	471/1053 = 1524 (30.9%)
EMPHASIS-HF	188/417 = 605 (31.1%)	332/702 = 1034 (32.1%)
SHIFT	544/1186 = 1730 (31.4%)	940/2113 = 3053 (30.7%)
I-PRESERVE	392/661 = 1053 (37.2%)	613/1176 = 1789 (34.3%)
CHARM-Preserved	190/509 = 699 (27.2%)	340/968 = 1308 (26.0%)

n/*n*, CV death/HF hospitalization; *N*, CV death or HF hospitalization (time-to-first event) or total number of CV deaths plus total number of HF hospitalizations (recurrent events). CV, cardiovascular; HF, heart failure.

Anker, McMurray. Eur Heart J 2012;33:2764-5

Acceptance of recurrent events as primary endpoint

- Commonly used in areas where mortality is relatively low (e.g., Multiple Sclerosis)
- ESC CV Round Table: "... particularly suitable for diseases where reductions in repeat hospitalizations are of interest (e.g. HF with preserved ejection fraction or acute decompensated HF). Regulatory and statistical guidance in this respect will be helpful to industry and academia."
- FDA precedence: In the HF area recurrent HFH has been used as primary endpoint for pivotal/late stage trials of devices (CHAMPION), gene therapies (CUPID-2) and more recently drugs (PARAGON)
- EMA (1999, 2015 draft) guidance for chronic HF acknowledges recurrent HFH as potentially acceptable primary endpoint in some circumstances highlighting the importance of terminal events for analysis and interpretation

How to capture treatment benefit in a recurrent event setting?

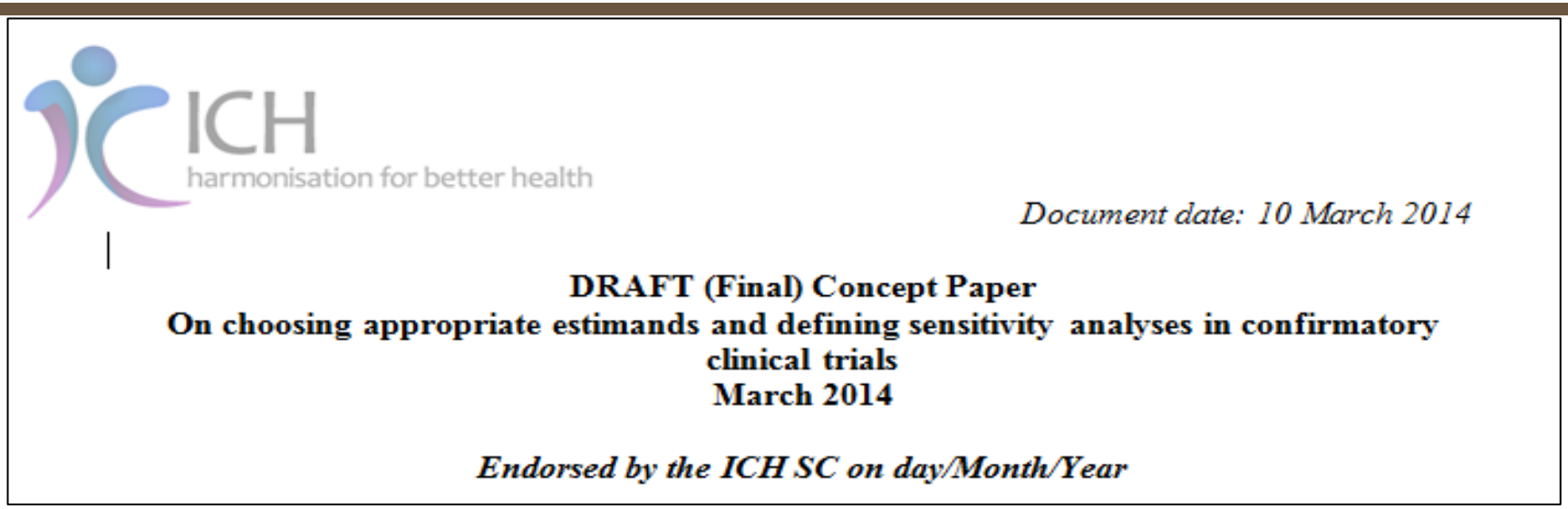
"The most typical source of bias involves fatal events – the worst patient outcome of death of course precludes all future events for that patient, while patients in less serious condition may remain on trial and realize many recurrent events. The bias will generally be in the direction of masking treatment effects."

(Tom Fleming)

How to capture treatment benefit in this setting where HFH rate is positively associated with risk of CV death?

→ Choice of estimand

Estimand framework


ICH
harmonisation for better health

Document date: 10 March 2014

DRAFT (Final) Concept Paper
On choosing appropriate estimands and defining sensitivity analyses in confirmatory clinical trials
March 2014

Endorsed by the ICH SC on day/Month/Year

Estimand framework clarifies distinction between

- target of estimation (estimand)
- method of estimation (estimator)

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Estimand – A proposed definition

An estimand reflects what is to be estimated to address the scientific question of interest posed by a trial.

The choice of an estimand involves:

- **Population of interest**
- **Endpoint of interest**
- **Measure of intervention effect**

Estimands in the context of recurrent events

Scientific Questions:

1. Does an experimental treatment reduce disease burden compared to control → Testing for between-group difference in the recurrent event occurrence / processes
2. By how much?
   Estimate the effect size compared to a control group

Population of interest:

- All randomized patients reflecting the target population

Endpoint of interest:

- Total HFH including first and subsequent events
- Composite of CV death and total HFH (CV death as 'final' recurrent event)
- CV death and HF hospitalization as co-primary outcomes

Measures of intervention effect for ‘total HFH’ or ‘composite endpoint of CV death and total HFH’

Measure of intervention effect:

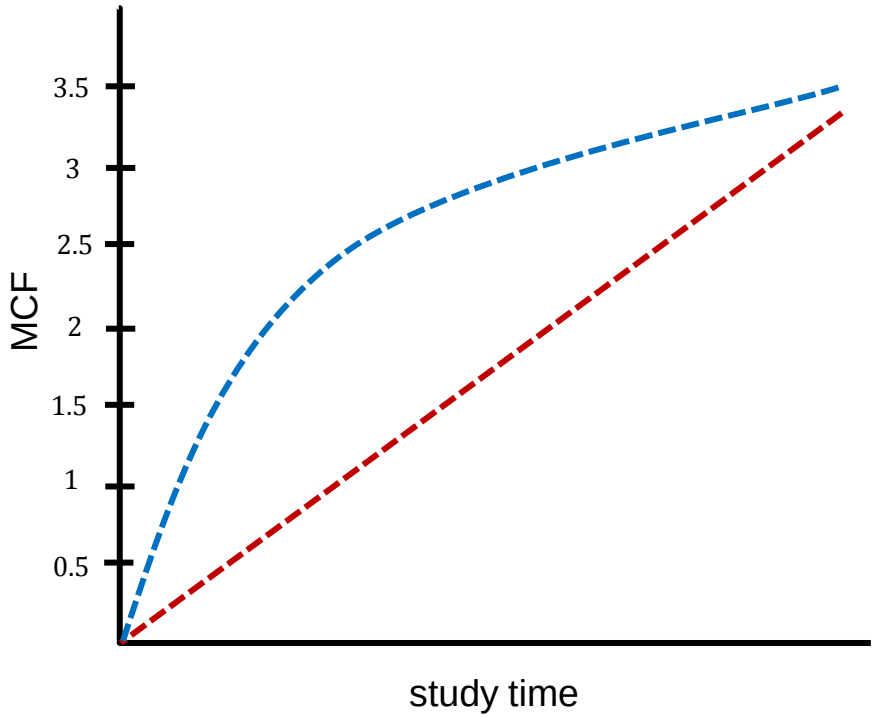
Parameter	Handling of death	
	Death as censoring	Death as terminal event
Mean ratio		
Rate ratio		
Intensity ratio / HR		

Death as censoring: interpretation conditional on being alive or assuming a latent process after death

Death as terminal event: acknowledging the fact that there will be no HFH after death

Mean cumulative function (MCF)

Mean **C**umulative **F**unction shows the mean number of recurrent events per subject by a certain time



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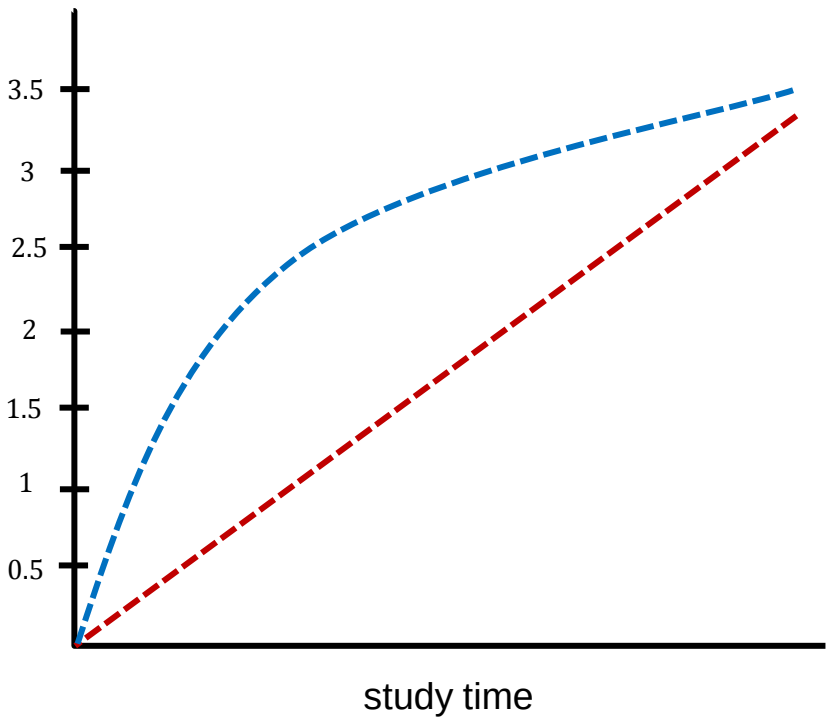
Rate function



Constant rate of events

Monotone increasing rate of events

- MCF $\mu(t) = \mathbb{E}\{N(t)\}$ changes as a function of time and its derivative $r(t)$ at a certain time point gives the rate function:

$$r(t) = \frac{\mathbb{E}\{dN(t)\}}{dt}$$

- Rate function can be interpreted as the average risk in a population at time t without conditioning on the event history
- When comparing two treatments one can look at mean ratios or rate ratios (or intensity ratios)

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Measures of intervention effect for ‘total HFH’ or ‘composite endpoint of CV death and total HFH’

Measure of intervention effect:

Parameter	Handling of death	
	Death as censoring	Death as terminal event
Mean ratio		
Rate ratio		

→ Various endpoints and measures of intervention effect, i.e., different combinations of parameter and handling of death, have been utilized in the cardiovascular literature

Parameter	Death	
	Censoring	Terminal
Mean Ratio		
Rate Ratio		

Conditional rate ratio

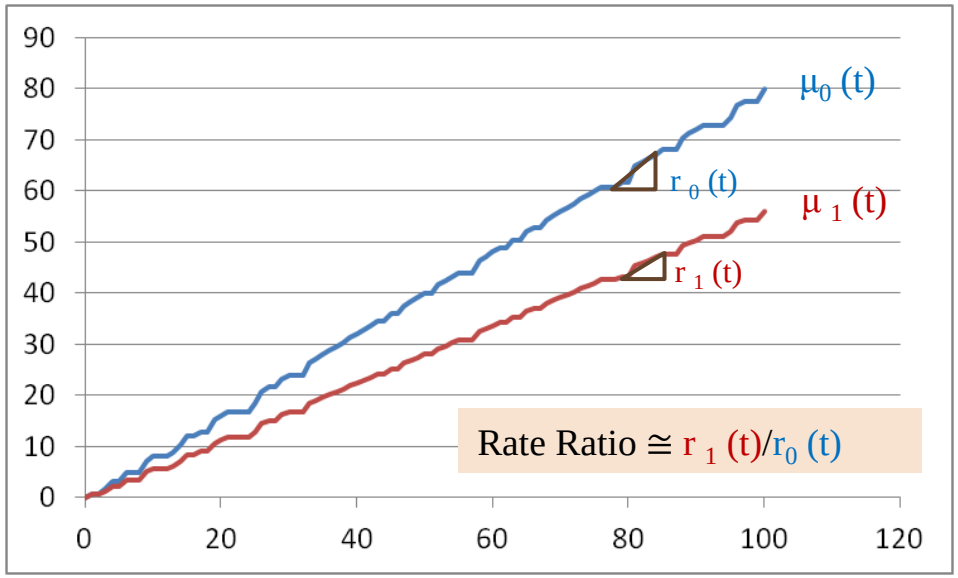
Primary endpoint: total HFH or composite of CV death and total HFH

Measure of intervention effect

Common rate ratio of composite endpoints in investigational group vs control group conditional on being alive (and at risk)

Estimation:

Proportional rate model based on general counting process could be useful (Lin, Wei, Ying and Yang, 2000)
Assumptions: proportional rates; marginal interpretation requires independent censoring



Time (days)

Solid lines: Nelson-Aalen estimators for mean functions $\mu_i(t)$

$$r(t \mid D \geq t, Z) = e^{\beta Z} r_0(t)$$

D = Death

e^{β} = treatment effect (Z=0 control, Z=1 test treatment)

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Parameter	Death	
	Censoring	Terminal
Mean Ratio		
Rate Ratio		

Marginal mean ratio

Primary endpoint: total HFH or composite of CV death and total HFH

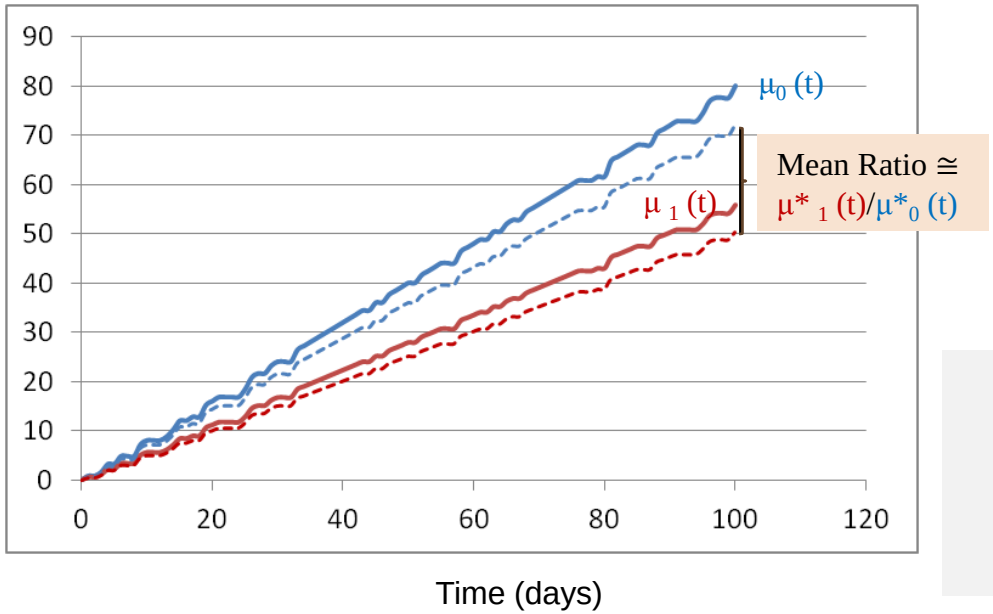
Measure of intervention effect

Marginal ratio of expected number of primary endpoint events in investigational group vs control group, acknowledging that there will be no HFH after death

Estimation:

Gosh & Lin (2000) or e.g. LWYY with censoring at end of study (Mao & Lin, 2015)

Assumption: Counting process continues after death and stays flat (no jumps) until end of the study



Solid lines: Nelson-Aalen estimators for mean functions $\mu_i(t)$

Dotted lines: Gosh & Lin estimators $\mu^*_i(t)$

=> adjust downwards

Favors treatments where more patients die early on and therefore may be less suitable for regulatory purposes

May be appropriate for cost analysis

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Marginal rate (or mean) ratio with latent process after death

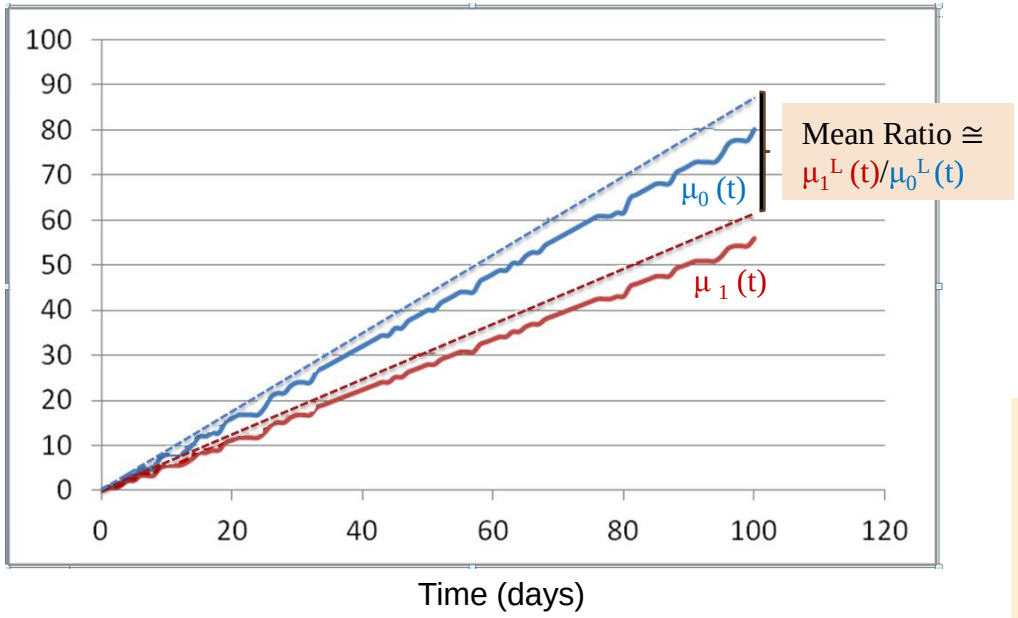
Parameter	Death	
	Censoring	Terminal
Mean Ratio		
Rate Ratio		

Primary endpoint: total HFH or composite of CV death and total HFH

Measure of intervention effect

Marginal rate ratio or ratio of expected number of primary endpoint events in investigational group vs control group assuming latent process continuing after death

Estmation:
Negative binomial model (NB; McCullagh and Nelder 1989) may be suitable
Assumptions: death as conditionally independent censoring (MAR), homogenous Poisson process for each subject, proportional intensity conditional on subject-specific frailty



Solid lines: Nelson-Aalen estimators for mean functions $\mu_i(t)$
Dotted lines: Estimators assuming counting process continues after death → adjust upwards in case of positive correlation

$$r(t|Z,U_i) = r_0 U_i \exp(\beta^T Z)$$

e^{β}: estimand for treatment effect (Z=0 control, Z=1 test treatment)
U_i=subject-specific random effect

Parameter	Death	
	Censoring	Terminal
Mean Ratio		
Rate Ratio		

Conditional rate ratio and hazard ratio

Co-primary endpoints: HFH and CV death

Measure of intervention effect

Rate ratio of recurrent HFH and **hazard ratio** of CV death conditional on subject-specific characteristics

Estimation:

- Joint frailty models which account for the correlation between the recurrent event process and the terminal event process
- Marginal interpretation of parameters is not straightforward, e.g. CV death HR from shared frailty model may be different from conventional Cox-regression-based HR
- May be sensitive to the choice of frailty terms

- $N_i(t) \mid U_i$ is a Poisson process with rate function $r(t \mid U_i) = r_0 \, exp\left(\beta_{1,trt_i}\right) U_i$
- $D_i \mid V_i$ is the terminal process with hazard rate $h(t \mid V_i) = h_0 \, exp\left(\alpha_{1,trt_i}\right) V_i$
- U_i and V_i are correlated random effects with mean 1 – usually gamma or log-normally distributed
- r_0 and h_0 are constant baseline rate/hazard functions
- $\{N_i(t), t > 0\} \sqcup D_i \mid U_i, V_i$

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Case-Study: ValHeFT – 1

A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER VALSARTAN IN CHRONIC HEART FAILURE

JAY N. COHN, M.D., AND GIANNI TOGNONI, M.D., FOR THE VALSARTAN HEART FAILURE TRIAL INVESTIGATORS*

N Engl J Med, Vol. 345, No. 23, December 6, 2001, pp 1667-1675

Study:

- Placebo-contolled study
- Placebo arm: 2499 patients and
- Valsartan arm: 2511 patients, i.e. total N=5010
- Mean duration of follow-up: 23 months
  (range: 0 – 38 months)

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Case-Study: ValHeFT – 2

Primary Outcomes:

- All-cause mortality
- Time to first event of a combined endpoint of all-cause mortality and morbidity
  (cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least four hours).

Results:

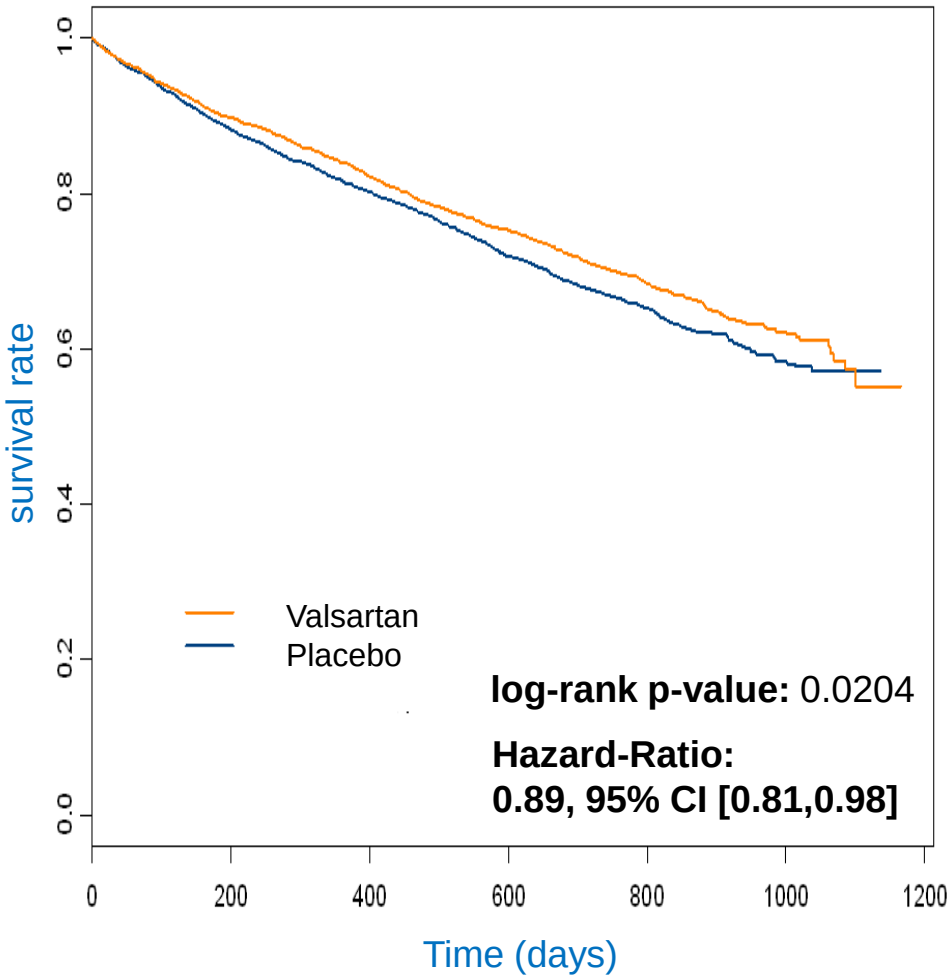
- All-cause mortality was similar in the two groups.
- Combined endpoint:
  - HR (Valsartan/Placebo): 0.87, 97.5% CI [0.77,0.97]; p-value: 0.009.

Post-hoc analysis

'Time-to-first event' analysis for composite of CV death / HFH

Composite Endpoint

CV death/ HF hospitalization



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Potential benefits of recurrent event data

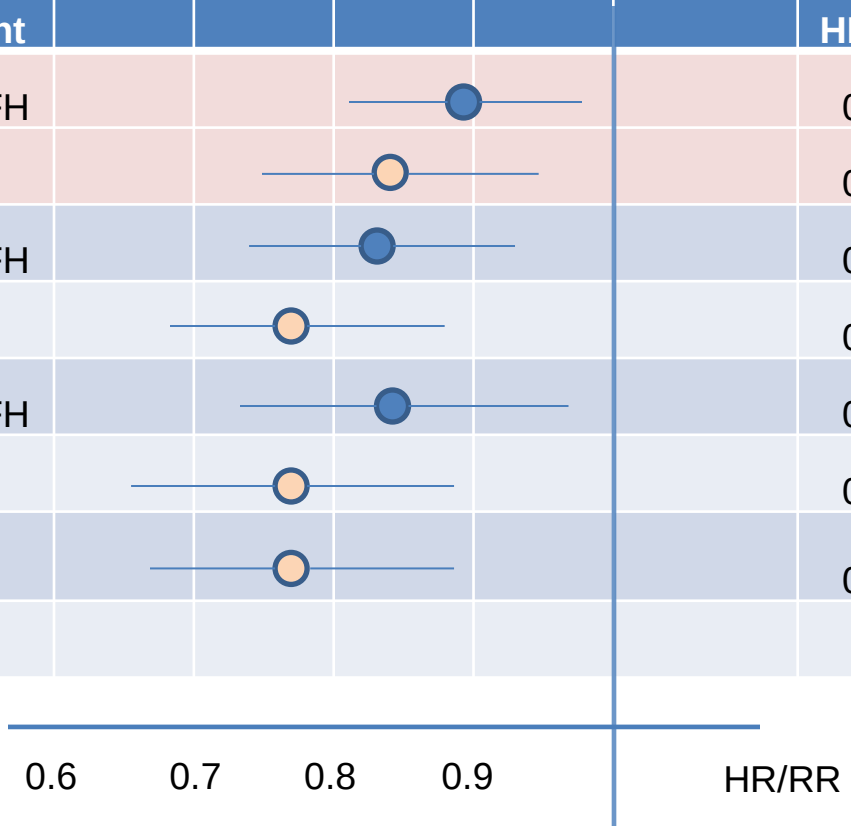
Time-to-first event approach (1610 events) ignores subsequent events

Number of HFH events	No. of patients PBO, NPBO=2499 N (%)	No. of patients Val, NVal =2511 N (%)	Total number of events NTOT =5010 N (%)
0	1878 (75.15)	1974 (78.61)	3852 (76.89)
1	344 (13.77)	317 (12.62)	661 (13.19)
2	146 (5.84)	130 (5.18)	276 (5.51)
3	56 (2.24)	51 (2.03)	107 (2.14)
4	36 (1.44)	19 (0.76)	55 (1.10)
5	21 (0.84)	13 (0.52)	34 (0.68)
≥6	18 (0.72)	7 (0.28)	25 (0.50)
Total number of HFH	**1189**	**922**	**2111**
Total number of CV deaths	**419 (16.77)**	**427 (17.01)**	**846 (16.89)**
Total number of composite 'first' events (HFH/CV death)	**841**	**769**	**1610**
Total number of composite 'rec.' events (HFH/CV death)	**1608**	**1349**	**2957**

Case Study: ValHeFT

Comparison of various approaches*

Method	Endpoint	HR/RR	95% CIL	95% CIU	p
TTFE	CVD/HFH	0.89	0.81	0.98	0.0204
	HFH	0.84	0.75	0.95	0.0034
LWYY	CVD/HFH	0.83	0.74	0.93	0.0012
	HFH	0.77	0.68	0.88	0.0001
NB	CVD/HFH	0.84	0.73	0.97	0.0176
	HFH	0.77	0.66	0.89	0.0007
Joint Frailty	HFH	0.77	0.67	0.89	0.0005
Gosh&Lin	HFH	NA	NA	NA	<0.0001



* based on investigator-reported HFH

CV death HR=1.01 (95% CI 0.89 – 1.16; p=0.8569)

Conclusions

- Recurrent events approaches have shown a reduction in total HFH in studies with large reduction in mortality (EMPHASIS, PARADIGM-HF) and in studies with no significant impact on mortality (CHARM-Preserved, SHIFT)
- Consensus on appropriate estimands would facilitate the recurrent event approach to play a larger role in future cardiovascular drug development (in particular in CHF)
- Composite M&M endpoint naturally extends the traditional TTFE approach and more fully captures the disease burden + may increase statistical power
- 'Marginal rate ratio of composite events with latent process after death' or the 'rate ratio of composite events conditional on being alive (and at risk)' could be meaningful measures of intervention effect

Conclusions

- Estimates for the composite endpoint have to be interpreted with caution if the number of deaths is non-negligible and treatment affects mortality
- Like in the case of time-to-first-event analysis, the quantification of treatment effects on individual components is essential for the interpretation of the results
- Alternative estimands/endpoints not discussed here:
  - WLW, PWP, Multi-state models
  - Win-Ratio approach (Pocock et al, 2011), non-parametric rank-based approaches
  - Days alive and out of hospital

References

- **Andersen, P. K. & Gill, R. D. (1982):** Cox's regression model for counting processes: a large sample study. Ann. Stat., 10, 1100–1120.
- **Andersen PK, Keiding N (2002):** Multi-state models for event history analysis. Statistical Methods in Medical Research 11: 91-115.
- **Cannon CP (1997):** Clinical perspectives on the use of composite endpoints. Controlled clinical trials 18:517-529.
- **Castaneda J, Gerritse B (2010):** Appraisal of several methods to model time to multiple events per subject: Modelling time to hospitalization and death. Revista Colombiana de Estadistica 33: 43-61.
- **Chi GYH (2005):** Some issues with composite endpoints in clinical trials. Fundamental & Clinical Pharmacology 19:609-619.
- **Cook R.J. (1995):** The design and analysis of randomized trials with recurrent events. Statistics in Medicine, Vol. 14, 2081-2098.
- **Cook RJ, Lawless JF (1997):** Marginal analysis of recurrent events and a terminating event. Statistics in Medicine, Vol 16, 911-924.
- **Cook RJ, Lawless JF, Lakhal-Chaieb L, Lee K-A (2009):** Robust estimation of mean functions and treatment effects for recurrent events under event-dependent censoring and termination: application to skeletal complications in cancer metastatic to bone. JASA, 104:485, 60-75.
- **Cowling BJ, Hutton JL, Shaw JEH (2006):** Joint modeling of event counts and survival times. Appl. Statist. 55, Part 1: pp 31-39.

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References (continued)

- **Freemantle N et al. (2003):** Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA Vol 289. No.19 2545-2575.
- **Freemantle N, Calvert M. (2007):** Weighing the pros and cons for composite outcomes in clinical trials. Journal of Clinical Epidemiology 60:658-659
- **Ghosh D & Lin DY (2000):** Nonparametric analysis of recurrent events and death. Biometrics, 56, 554–562.
- **Ghosh D & Lin D Y (2002):** Marginal regression models for recurrent and terminal events. Statistica Sinica, 12, 663–688.
- **Li QH, Lagakos SW (1997):** Use of Wei-Lin-Weissfeld Method for the Analysis of a Recurring and Terminating Event. Statistics in Medicine 16: 925-940.
- **Lin, D. Y., Wei, L. J., Yang, I. & Ying, Z. (2000):** Semiparametric regression for the mean and rate functions of recurrent events. J. R. Stat. Soc., B, 62, 711–730.
- **Liu L, Wolfe RA, Huang X (2004):** Shared frailty models for recurrent events and terminal event. Biometrics 60: 747-756
- **McCullagh P, Nelder JA (1989):** Generalized Linear Models, 2nd edn. London: Chapman and Hall
- **Metcalfe C et al (2003):** The use of hospital admission data as measure of outcome in clinical studies of heart failure. European Heart Journal 24: 105-112

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References (continued)

- **Metcalfe C, Thompson SG (2006):** The importance of varying the event generation process in simulation studies of statistical methods for recurrent events. Statistics in Medicine 26: 165-179.
- **Metcalfe C, Thompson SG (2007):** Wei, Lin and Weissfeld‘s marginal analysis of multivariate failure time data: should it be applied to a recurrent events outcome) Statistical Methods in Medical Research 16: 103-122.
- **Montori VM, et al., (2005):** Validity of composite end points in clinical trials. BMJ Vol 330 2005.
- **Neaton JD, Gray G, Zuckerman BD, Konstam M, (2005):** Key issues in end point selection for heart failure trials: composite end points. Journal of Cardiac Failure Vol.11 No. 8 2005.RTG
- **Pocock S. J., Ariti C. A., Collier T. J., and Wang D. (2011):** The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European heart journal.
- **Prentice R. L., Williams B. J., and Peterson A. V. (1981):** On the Regression Analysis of Multivariate Failure Time Data. Biometrika, 68, 373–379.
- **Schaubel DE, Zhang M (2010):** Estimating treatment effects on the marginal recurrent event mean in the presence of a terminating event. Lifetime Data Analysis 16: 451-477.
- **Wei L., Lin D. & Weissfeld L. (1989):** Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions. Journal of the American Statistical Association, 84, 1065–1073.
- **Zeng D, Lin DY (2009):** Semiparametric transformation models with random effects for joint analysis of recurrent and terminal events. Biometrics 65: 746-752.

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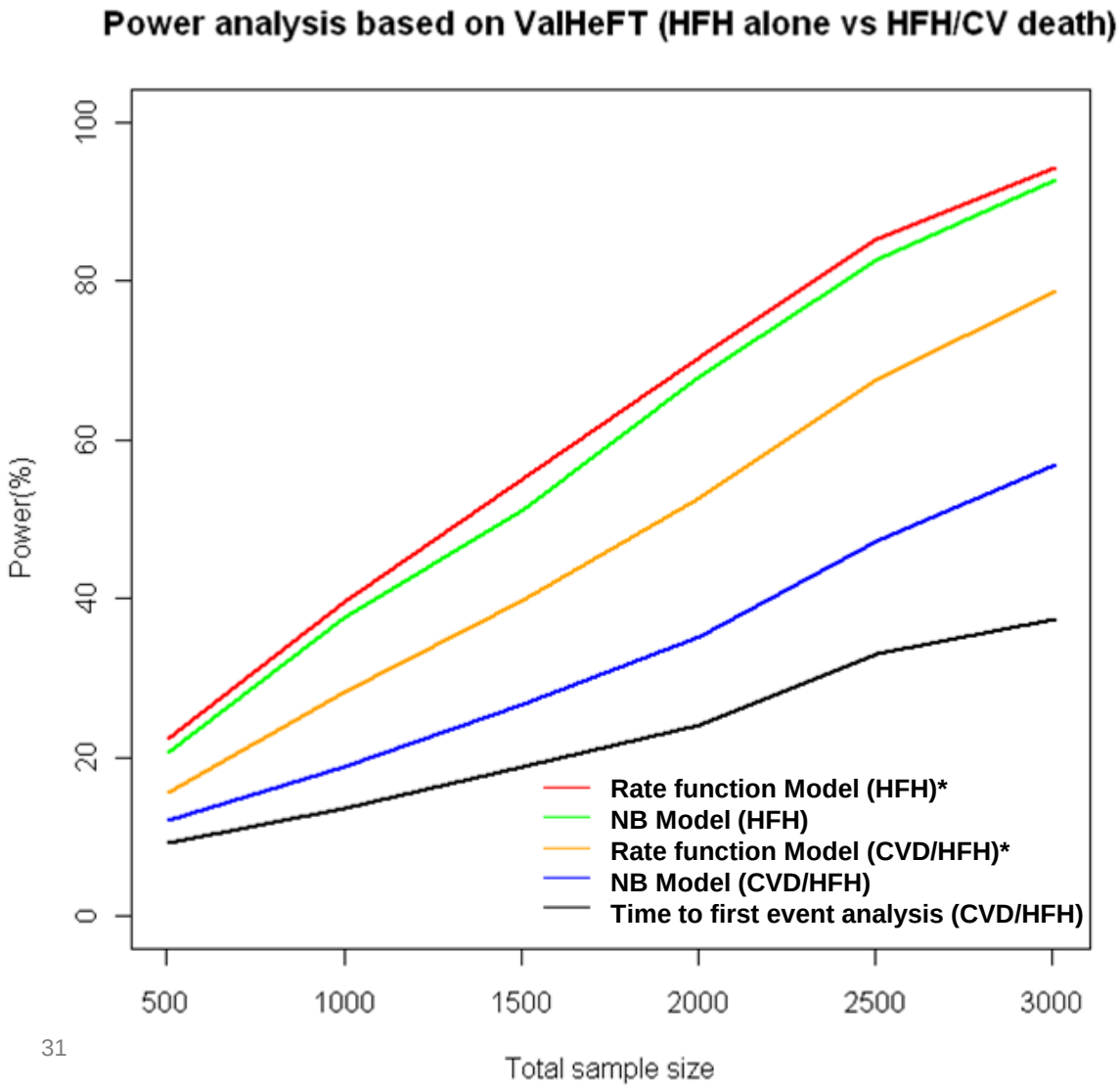
Potential benefits of recurrent event analysis

Inclusion of all HF hospitalizations may lead to increased power



For each given sample size, 1000 bootstrap samples were drawn from ValHeFT data – a placebo-controlled study, N=5010, mean follow-up 23 months, max 38 months data

***L**in, **W**ei, **Y**ang, & **Y**ing (2000)

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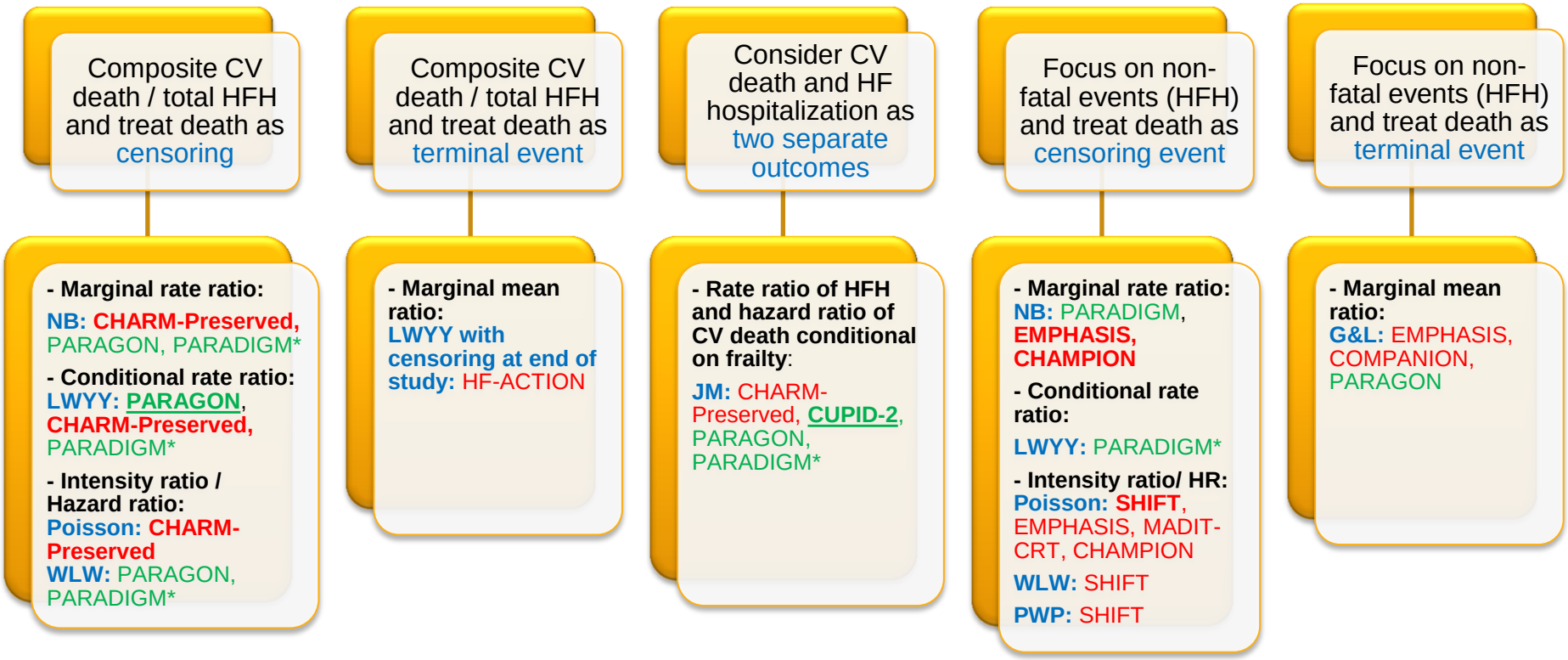
Overview of estimands and analysis methods used in selected CHF trials



Green color indicates pre-specification, red color post-hoc analyses. **Bold red indicates primary post-hoc analysis approach**, **bold green and underlined indicates pre-specified primary endpoint analysis approach**

* Not published yet

NB: Negative binomial model

LWYY: Proportional rate model based on general counting process

G&L: Mean cumulative incidence function model "adjusted for death as terminal event"

JM: Joint model for recurrent and terminal events with shared frailty

PWP: Proportional hazards gap time model

WLW: Multivariate failure time analysis based on proportional hazards

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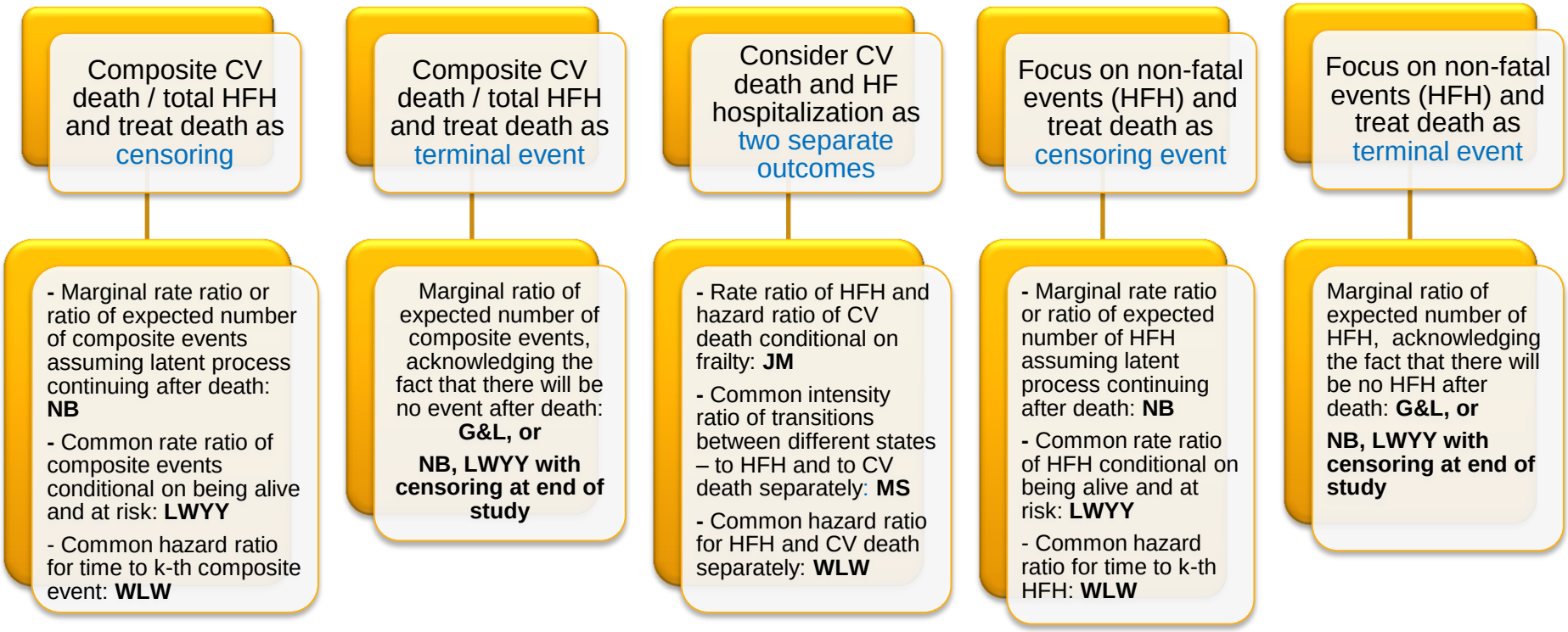
Overview of some Recurrent Event Approaches, Measures of Intervention Effect and Analysis Methods



NB: Negative binomial model
LWYY: Proportional rate / mean cumulative incidence function model based on general counting process
WLW: Multivariate failure time analysis based on proportional hazards
JM: Joint model for recurrent and terminal events with shared frailty
G&L: Mean cumulative incidence function model "adjusted for death as terminal event" / cause-specific rate function
MS: Multistate model

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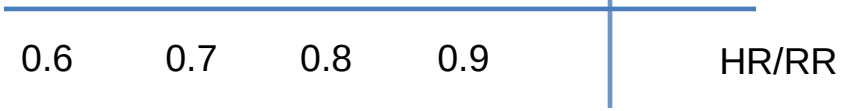
Case Study: PARADIGM

Comparison of various analysis approaches

Method	Endpoint	HR/RR	95% CIL	95% CIU	p
TTFE	CVD/HFH	0.80	0.73	0.87	<0.0001
	HFH	0.79	0.71	0.89	<0.0001
LWYY	CVD/HFH	0.79	0.71	0.87	<0.0001
	HFH	0.78	0.68	0.90	0.0005
NB	CVD/HFH	0.76	0.67	0.85	<0.0001
	HFH	0.77	0.67	0.89	0.0004
Joint Frailty	HFH	0.75	0.65	0.87	0.0001



CV death HR=0.80 (95% CI 0.71 – 0.89)

Estimands and analysis methods used in other cardiovascular trials

Trial	Indication	Endpoint	Estimand	Method	
TRITON-TIMI38[1]	ACS	Total composite of CV death, MI and stroke	Rate Ratio	Poisson regression	Post-hoc
ACTIV-I[2]	AFib	Composite of (1) Stroke, MI, or vascular death, (2) same as (1) plus HFH	Rate Ratio	LWYY	Secondary
PROVE-IT TIMI 22[3]	Lipid-lowering	Composite of death, MI, UA requiring re-hospitalization, stroke, or revascularization	Rate Ratio	Posson regression	Post-hoc
IDEAL[4]	Lipid-lowering	Composite of CHD death, MI, resuscitated cardiac arrest, stroke, revascularization, hospitalization for UA, HFH, and PAD	Hazard Ratio fro time to 1st, 2nd, ..5th event	WLW	Post-hoc

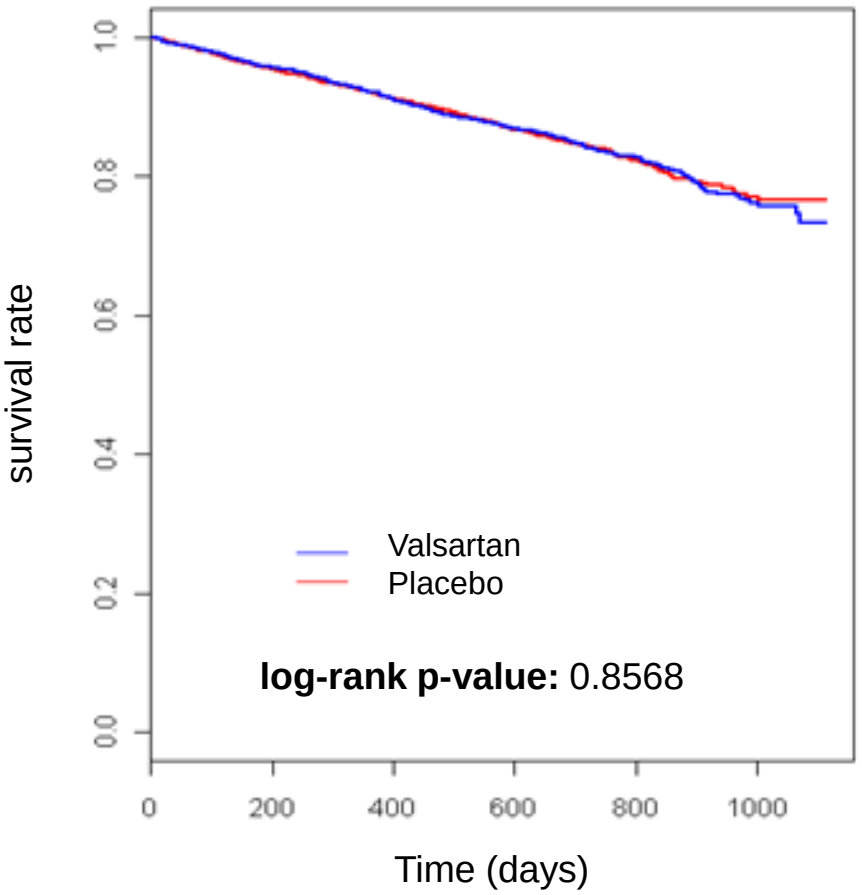
[1] Murphy, 2008, [2] Yusuf, 2011, [3] Murphy, 2009, [4] Tikkanen, 2009

Case Study: ValHeFT

N Engl J Med, Vol. 345, No. 23, December 6, 2001, pp 1667-1675

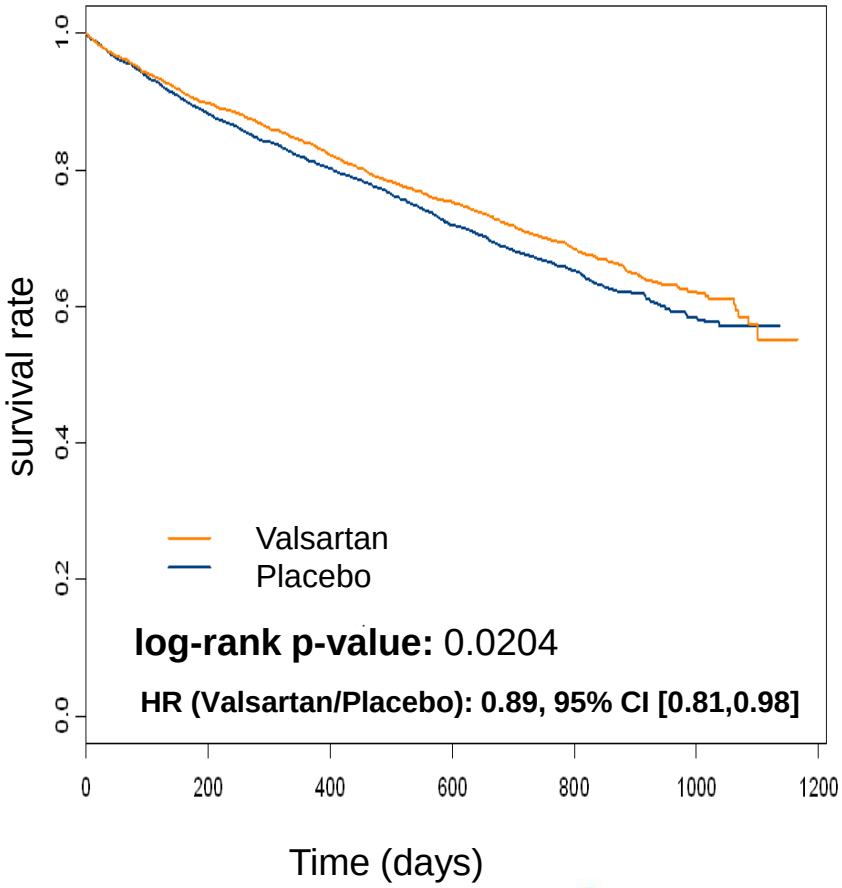
Placebo-controlled study, N=5010, mean duration of follow-up 23 months (range, 0 to 38 months).

CV death



Composite Endpoint

CV death / HFH



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Recurrent events approach utilizes substantially more events than time to first-event analysis

Table I Number of events in 'time-to-first event' analysis and 'recurrent events' analysis of heart failure trials

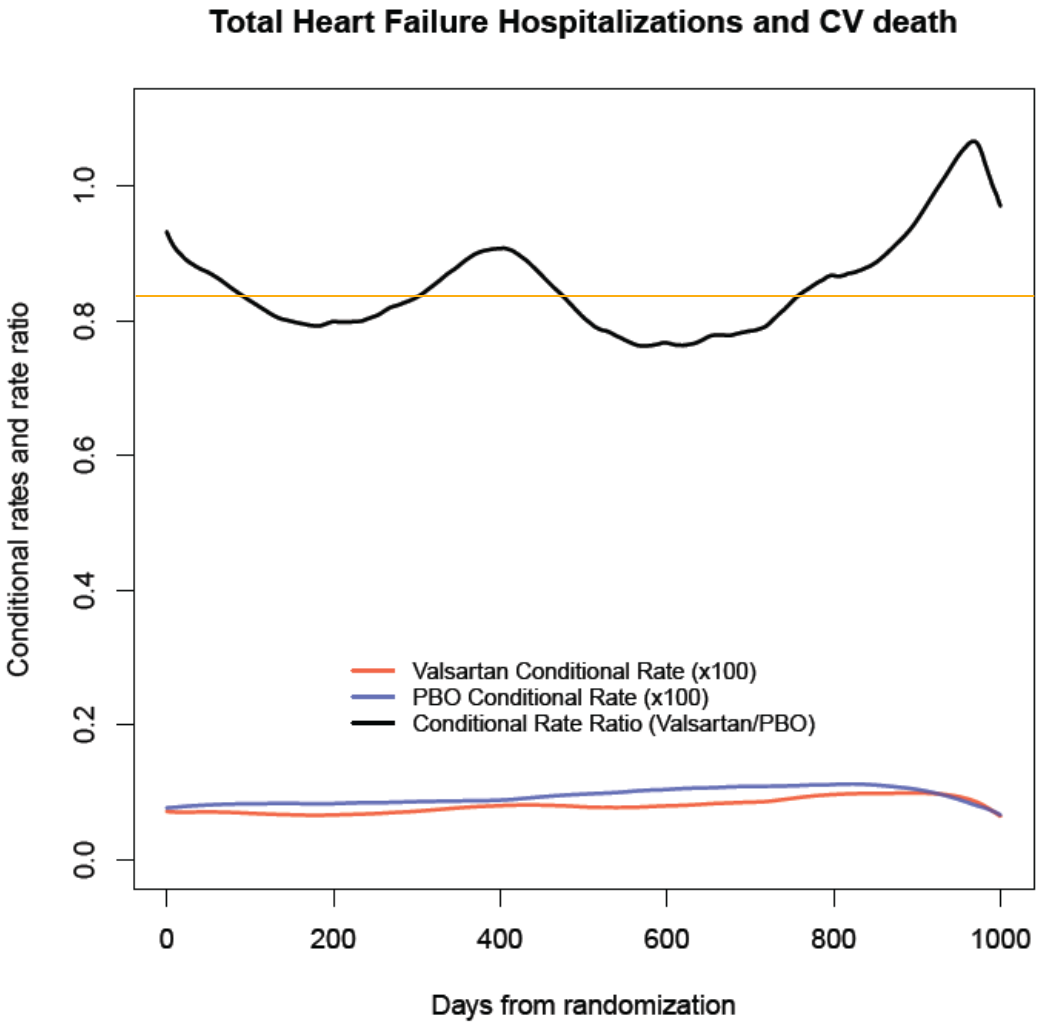
Trial	Time-to-first-event (CV death or HF hospitalization): CV death as % of primary outcome (*n*/*n* = *N*)	Recurrent events (all CV deaths and all HF hospitalizations): CV death as % of all events (*n*/*n* = *N*)
CHARM-Added	316/705 = 1021 (31.0%)	649/1443 = 2092 (31.0%)
CHARM-Alternative	237/503 = 740 (32.0%)	471/1053 = 1524 (30.9%)
EMPHASIS-HF	188/417 = 605 (31.1%)	332/702 = 1034 (32.1%)
SHIFT	544/1186 = 1730 (31.4%)	940/2113 = 3053 (30.7%)
I-PRESERVE	392/661 = 1053 (37.2%)	613/1176 = 1789 (34.3%)
CHARM-Preserved	190/509 = 699 (27.2%)	340/968 = 1308 (26.0%)
ValHeFT	**461/1149=1610 (28.6%)**	**846/2111=2957 (28.6%)**

n/*n*, CV death/HF hospitalization; *N*, CV death or HF hospitalization (time-to-first event) or total number of CV deaths plus total number of HF hospitalizations (recurrent events). CV, cardiovascular; HF, heart failure.

Anker, McMurray. Eur Heart J 2012;33:2764-5

Case Study ValHeFT

Smoothed estimates of conditional rate function and conditional rate ratio



Common rate ratio conditional on being alive and at risk = 0.83

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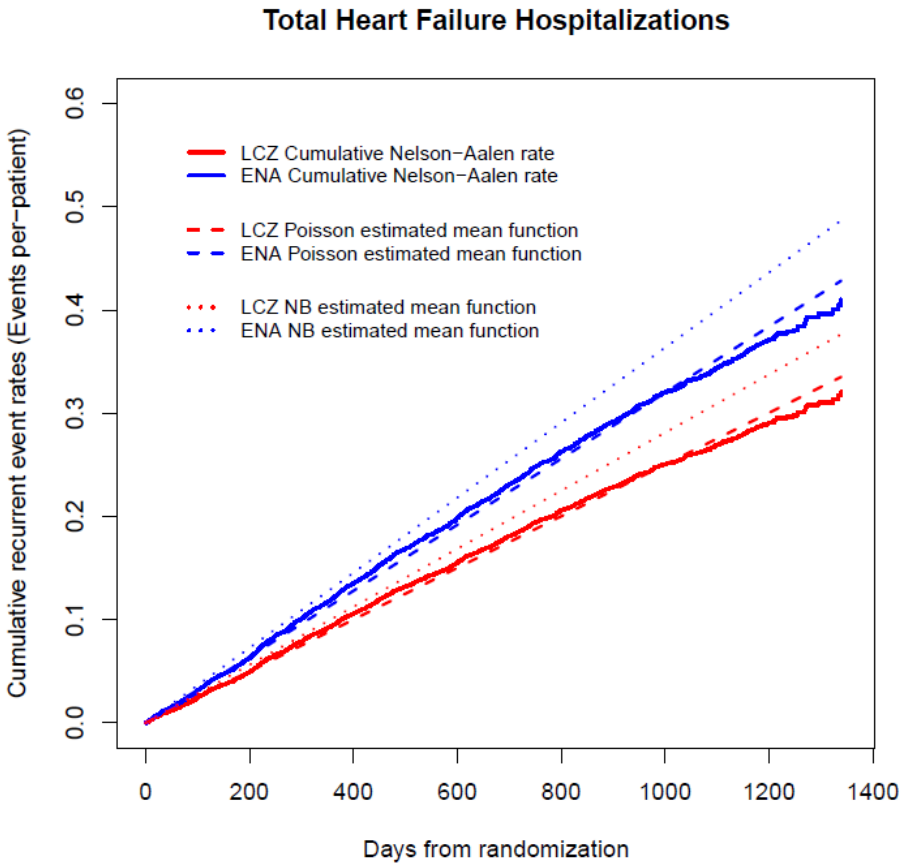
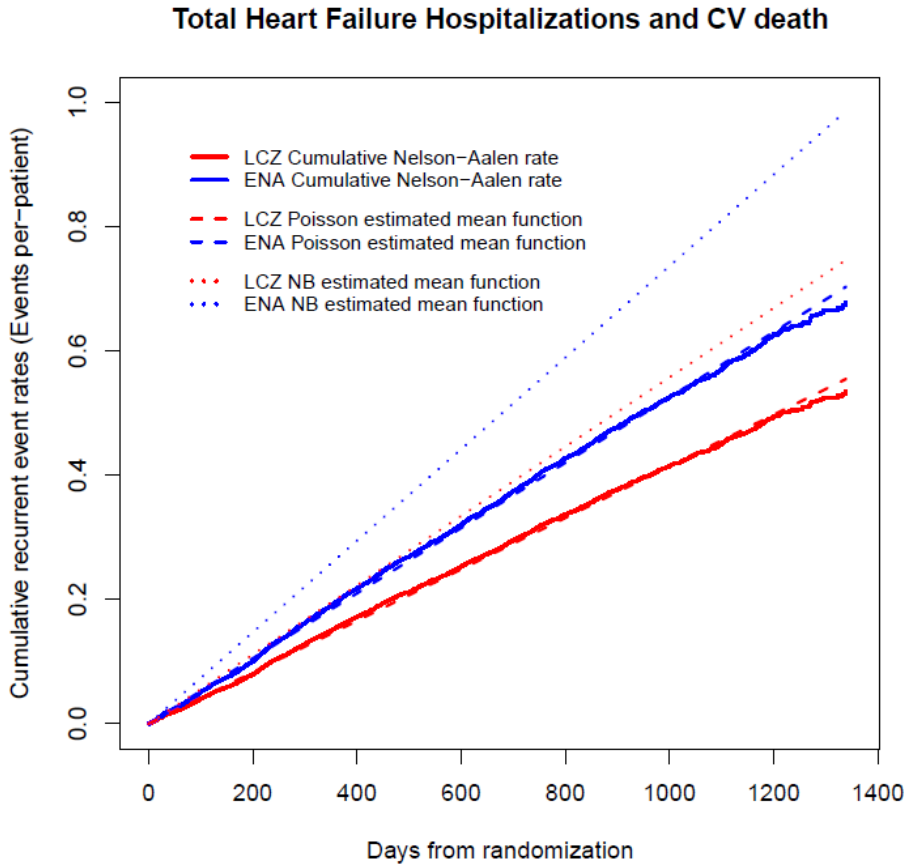
Case Study ValHeFT

Poisson and negative binomial estimates of mean function





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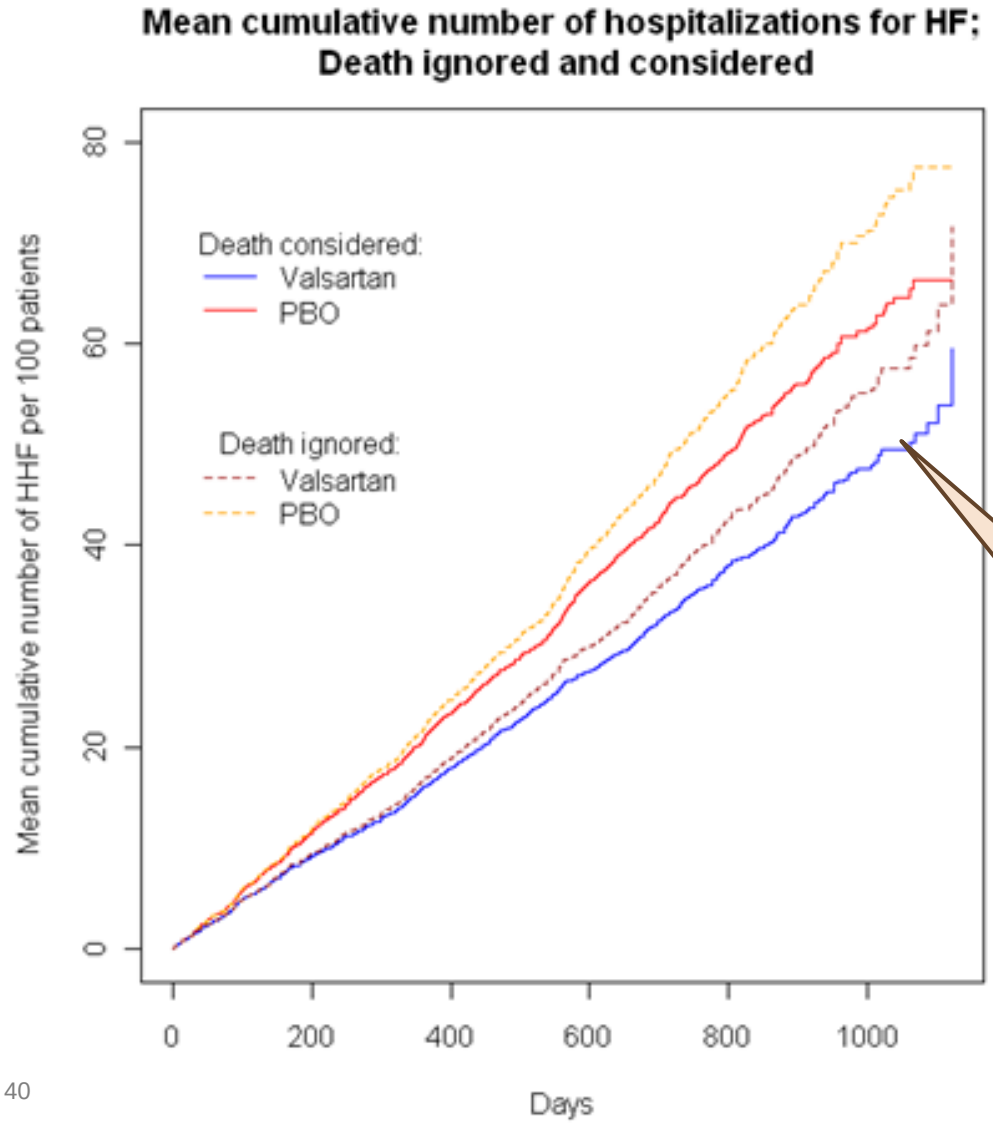
Case Study: ValHeFT

Non-parametric analysis (Ghosh & Lin, 2000) for mean cumulative number of events with death as terminal event



Mean function adjusted downwards since patients who died cannot be hospitalized anymore.

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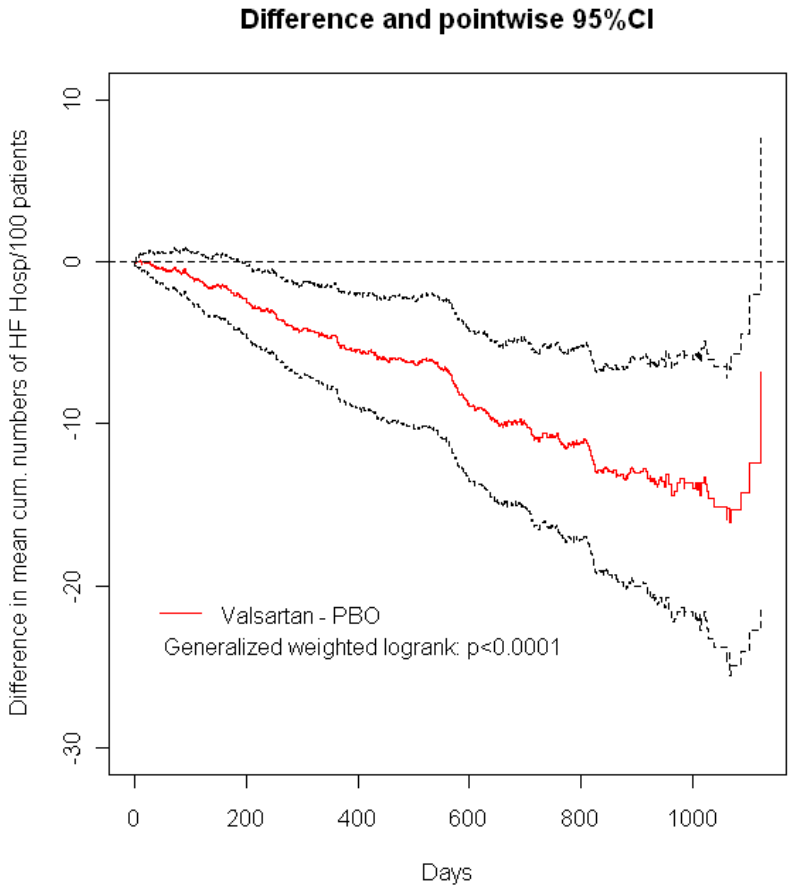
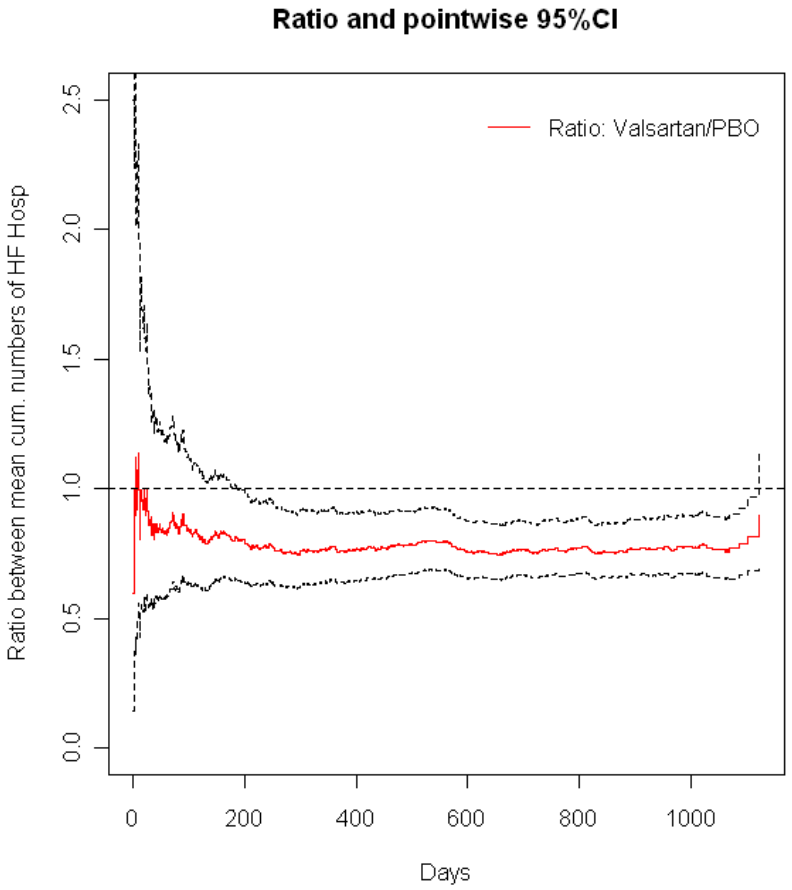
Case Study: ValHeFT

Non-parametric analysis (Ghosh & Lin, 2000) for mean cumulative number of events with death as terminal event





Case Study: ValHeFT

Parametric joint modeling applied to ValHeFT

$N_i(t) \mid U_i$ is a counting process with rate function $r(t \mid U_i) = \lambda_0 \exp(\beta_{1,trt_i}) U_i$

$D_i \mid V_i$ is the terminal process with hazard rate $h(t \mid V_i) = h_0 \exp(\alpha_{1,trt_i}) V_i$

U_i and V_i are random effects with mean 1

$\{N_i(t), t > 0\} \sqcup D_i \mid U_i, V_i$

λ_0 and h_0 are constant baseline rate/hazard functions.

Log-normal distributed frailties	Parameter	$V_i = U_i$	$V_i = U_i^{\psi}$	U_i, V_i follow bivariate dist.
Change in hospitalization rate due to treatment	$\exp(\beta_{1,Val})$	0.771 p-val=0.0005	0.765 p-val=0.0006	0.774 p-val=0.0003
Change in CV-death hazard rate due to treatment	$\exp(\alpha_{1,Val})$	1.013 p-val=0.8908	1.009 p-val=0.9093	1.012 p-val=0.8860

Gamma distributed frailties	Parameter	$V_i = U_i$	$V_i = U_i^{\psi}$
Change in hospitalization rate due to treatment	$\exp(\beta_{1,Val})$	0.770 p-val=0.0003	0.769 p-val=0.0005
Change in CV-death hazard rate due to treatment	$\exp(\alpha_{1,Val})$	1.012 p-val=0.8951	1.014 p-val=0.8682

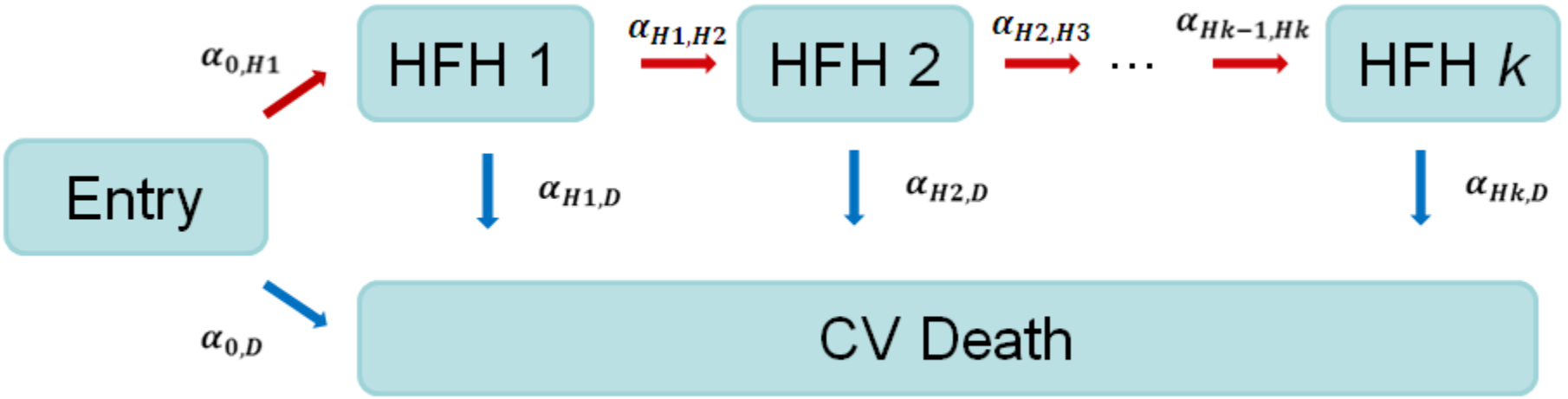
Nelson-Aalen Estimator

- $\Lambda_0(t)$ arbitrary mean function
- $Y_i(t)$ indicates whether subject i is 'at risk' at time t
- $Y_\Sigma(t) = \sum_{i=1}^{m} Y_i(t)$ are the total number of patients at risk over $[t, t+dt)$
- $dN_\Sigma(t) = \sum_{i=1}^{m} Y_i(t) dN_i(t)$ are the total number of events observed over $[t, t+dt)$
- $t_{(1)}, \ldots, t_{(H)}$ denote the H distinct event times across all m patients

The Nelson-Aalen Estimator is then given by

$$\Lambda_0(t) = \sum_{\{h | t_{(h)} \leq t\}} \frac{dN_\Sigma\left(t_{(h)}\right)}{Y_\Sigma\left(t_{(h)}\right)}$$

Common intensity ratio of transitions between different states - Multistate Model



Estimand

Common intensity ratio of transitions between different states (can be implemented as stratified Cox regression model with or without inclusion of transition to CV death as an event)

Marginal interpretation of parameters is not straightforward

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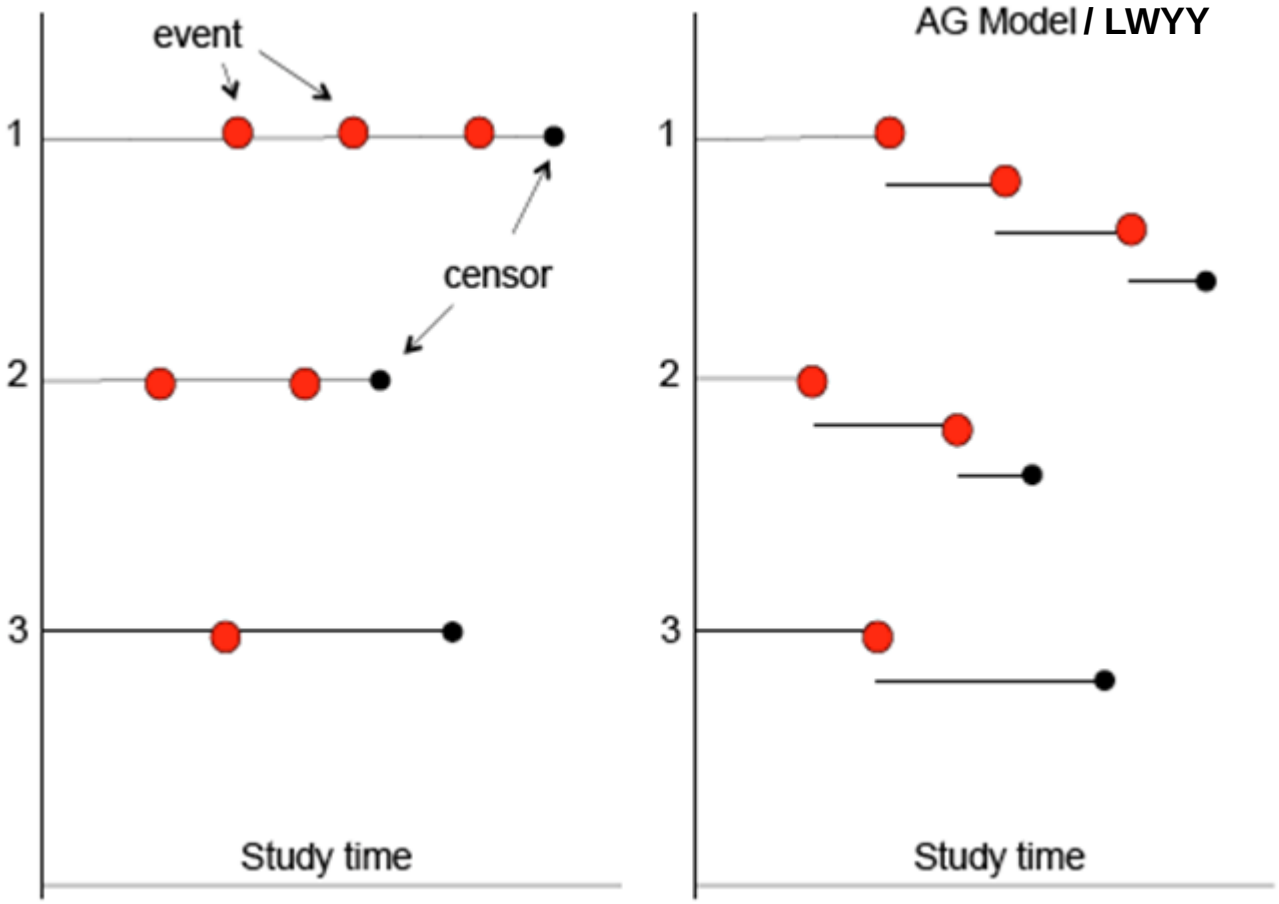
Modelling Recurrent Event Data – LWYY
(Lin, Wei, Yang and Ying, 2000)



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LWYY: Proportional rate / mean cumulative incidence function model (Lin, Wei, Yang and Ying, 2000)

- $N_i(t)$ is a general counting process and the rate function is given by

$$r(t) = \lambda_0(t)\exp(\beta^T Z_i)$$

  where $\lambda_0(t)$ is the unspecified baseline rate function

- Mean number of events by time t is given by

$$\mu(t) = \int_0^t r(s)\,ds = \exp(\beta^T Z_i)\int_0^t \lambda_0(s)ds = \exp(\beta^T Z_i)\,\Lambda_0(t)$$

- $\Lambda_0(t)$ can be estimated through the Nelson-Aalen estimator
- For estimation of regression coefficients the same partial likelihood score functions as for the **Andersen-Gill** model are used, but Poisson process assumption is relaxed
- A robust sandwich variance estimate is used to account for dependence of recurrent events on the same subject (e.g. PROC PHREG in SAS can be used)
- Estimates the common rate ratio of events in the interventional group relative to control group conditional on being at risk. Marginal (unconditional) interpretation requires independent censoring assumption to hold.
- Within treatment rates are time-dependent and can be graphically displayed (Nelson-Aalen estimator). Rate ratio assumed constant over time and common across recurrent events.

Shared frailty model: Joint model for recurrent and terminal events (Cowling et al, 2006; Zeng & Lin, 2009; Liu et al, 2004)

- $N_i(t) \mid U_i$ is a counting process with rate function

$$r(t \mid U_i) = \lambda_0(t) \exp(\beta^T Z_i)\, U_i$$

where $\lambda_0(t)$ is an arbitrary baseline rate function.

- $D_i \mid V_i$ is the terminal process with hazard rate

$$\mathrm{h}(t \mid V_i) = h_0(t) \exp(\alpha^T Z_i)\, V_i$$

where $h_0(t)$ is an arbitrary baseline hazard function and ψ an unknown constant.

- U_i, V_i are correlated frailty terms (follow bivariate dist., parametrized through γ), such that

$$\{N_i(t), t > 0\} \; independent \; of \; D_i \mid U_i, V_i, Z_i$$

- Common choices for the distribution of U_i, V_i are the log-normal and gamma distribution.
- Maximization of the joint likelihood requires numerical integration techniques

$$L_{N_i(t),D_i}(\alpha, \beta, \gamma, \psi) = \int p_{N_i(t)\,|U_i}(\beta) \;\; p_{D_i|\,V_i}(\alpha, \psi) \;\; p_{(U_i,V_i)}(\gamma)\; \mathrm{d}u_i \mathrm{d}v_i$$

- Estimated rate ratio of recurrent events is conditional on subject-specific frailty (U_i, V_i), i.e. marginal interpretation not straightforward
- R package «frailtypack» can be used to fit the model using arbitrary baseline rate and hazard / SAS PROC NLMIXED can be used to fit the model using parametric models for the baseline rate and hazard

Negative Binomial (Mixed Poisson) Model

- $N_i(t) \mid U_i$ is a Poisson process; U_i is a gamma distributed, with mean *1* and variance ϕ
- Instantaneous probability of an event occuring is given by the rate function

$$r(t|U_i) = \frac{\mathbb{E}\{dN_i(t)\,|\,U_i\}}{dt} = \frac{\Pr(dN_i(t)=1\,|\,U_i)}{dt} = \lambda_0 U_i \exp(\beta^T Z_i)$$

  where λ_0 is the constant baseline rate

- Mean number of events by time t is therefore given by

$$\mu(t|\,U_i) = \int_0^t r(s|\,U_i)\,ds = \lambda_0 U_i \exp(\beta^T Z_i)\,t$$

- Marginally, we obtain

$$\mu(t) = \mathbb{E}\{N_i(t)\} = \lambda_0 \exp(\beta^T Z_i)\,t \quad \text{and} \quad \mathbb{V}\mathrm{ar}\{N_i(t)\} = \mu(t)\,(1+\phi\,\mu(t))$$

- Estimates the common rate ratio of events in the interventional group relative to control group. Allows to estimate mean hospitalization rate for each treatment arm separately.
- Easy to understand and implement (PROC NLMIXED, GLIMMIX, GENMOD in SAS).
- **Assumes conditionally independent censoring (i.e. censoring is conditionally independent of the counting process, given covariates and measurement history). Corresponds to general concept of 'missing at random' (MAR).**

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Mean cumulative incidence function model "adjusted for death as terminal event" (Ghosh and Lin, 2000, 2002)

- $N_i(t)$ is the actual number of events that subject i has experienced by time t in the presence of death and D_i is the time of death
- **Marginal mean function** $m(t)$ in presence of death is used to quantify frequency of recurrent events, **acknowledging the fact that subjects cannot experience recurrent events after death**

$$m_i(t) = \int_0^t S_i(u)\ r_i(u)\ du$$

where $S_i(t) = \Pr(D_i \geq t)$ and $r_i(t) = \frac{\mathbb{E}(dN_i(t)|D_i \geq t)}{dt}$

- An estimators for $m(t)$ can be obtained through integration of the product of Kaplan-Meier and Nelson-Aalen estimators
- Comparing mean frequency functions for two treatments arms can be based on a generalized log-rank statistic L_R with appropriate weights
- Assessing the treatment effect with respect to both the recurrent events and survival times requires simultaneous testing on both endpoints, which can be accomplished by using a combined test statistic (weigthed sum of L_R and log-rank statistic for testing equality of survival times).
- Currently not implemented in statistical software (SAS, R).